D.2	Antituberculosis formulations deletions
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The overall rationale for this application is to harmonise the EML/c with the WHO Stop TB Partnership' treatment guidance and Global Drug Facility. The principle is to concentrate listing of TB medicines on a limited number of the key drug formulations that provide optimal treatment across all the relevant age ranges.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Oral liquid/syrup child formulations of ethambutol, isoniazid and pyrazinamide are proposed to be removed. The rationale is that the WHO strategy is now to focus on the development of a limited range of dispersible tablet formulations for children, due to enhanced simplicity and cost of procurement, storage and dispensing. The relevant DTs for ethambutol and isoniazid were added to the WHO EML Core list in 2019 (and the removal of these oral liquids were planned for removal in 2021). The Fixed Dose Combination of Isoniazid + Pyrazinamide +Rifampicin is also proposed for removal as no quality assured supplier of this formulation has been identified and FDCs containing the above medicines+ Ethambutol are already listed on the EML (which lowers the pill burden for standard 4 drug treatment of drug susceptible TB). Other formulations of Amikacin, amoxicillin/clavulanate, ethionamide and linezolid are also proposed to be removed from the Complementary list of the EML/c. These include formulations that are either redundant in terms of current TB Guidance and/or no quality assured formulation has been identified. For Amikacin the formulation of 250 mg/mL in a 2 ml vial is proposed to be <u>added</u> to the Complementary List of the EML/c. The WHO now recommend an all oral approach to the treatment of Drug Resistant (DR-TB) and amikacin is reserved for when oral options are not possible. Given its limited use and that the 250 mg formulation is available from the STBP GDF and is on the Access antibiotic EML/c, listing one Amikacin formulation follows the principle of simplification. Following the same principles as above, as there are already listed oral DTs of linezolid, the proposal is to delete the iv formulation of linezolid. The non-DT version of Ethionamide is also proposed to be deleted as a DT preparation is available. A similar process has been applied to co-amoxicillin preparations, where harmonisation with the Access list and avoidance of lower concentration/higher volume child formulations has led to the suggestion to delete co-amoxicillin 125 mg/31.5 as the formulation 250mg/62.5 is already on the EML/c. The WHO STBP GDF also has a goal to only list the key specific formulations required for isoniazid and ethambutol rather than across wide dosing ranges, focussing on the Ethambutol 100 mg and 400 mg tablets and for Isoniazid the 100 mg and 300 mg tablets.

Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☐ No ☒ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Details of the PK equivalence is provided in the STBP guidance. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? yes
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☐ No ☒ Not applicable Comments: Details of the relevant safety of the medicines are provided in the WHO TB treatment guidance, but these applications focus on changes in the quality-assured formulations.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☐ No ☒ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	See above
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	See above

Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☐ No ☒ Not applicable Comments:
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☐ No ☒ Not applicable Comments: See above
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: WHO TB Treatment Guidelines 2017.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	It should be noted that although the application very appropriately focusses the EML/c on the key drugs and formulations to treat drug susceptible and resistant TB, there are only a limited number of suppliers of WHO-Prequalified (PQed) medicines as discussed in this application (eg 2 for PZ 150 mg DT, one for INH and MBT etc.
Any additional comments	It would be prudent for the EML/c to monitor the impact of any changes in listing on drug availability in the future.
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	All of the recommendations put forward from the WHO GTB programme are reasonable and appropriate. The clear goal here is to concentrate efforts on a smaller number of specific formulations that provide optimal treatment options for children and adult DR/DS TB, aligning with the EML listing for other antibacterial treatment. Although it could be anticipated that this would lead to wider range of generic companies producing these key formulations, a potential concern would be that global provision would be concentrated on a small number of providers, with very limited alternatives for treatment available if there was an interruption of supply.
References (if required)	